

Skin manifestations in sarcoidosis

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Almost a century ago, the relationship of sarcoid infiltrations of the skin and granulomatous changes in other organs was recognised. Schaumann, in 1914, proposed that lupus pernio (fig. 1a–c) could be a manifestation of a generalised disease. Later on, a variety of skin manifestations have been described to occur more or less frequently. Lupus pernio indicates an unfavourable prognosis, whereas in the case of erythema nodosum (EN) (fig. 2), disease remission generally occurs within months or a few years [1–4]. The histopathological characteristics of the two findings are totally different, reflecting the variable clinical picture and outcome in this inflammatory disorder where the antigen(s) still are unknown [5, 6]. Beside these two extremes, there are a number of other more or less common skin lesions having either a maculopapular, subcutaneous, cicatricial or plaque character. In this chapter, a sharp distinction will be made between nonspecific lesions, *i.e.* erythema nodosum, and specific skin manifestations, *e.g.* lupus pernio.

The frequency of skin lesions in sarcoidosis varies depending on the intensity by which they are looked for [7, 8], as well as on the ethnic background of the patients [5, 6]. In Scandinavia, about one-third of the patients born there will present with EN as part of Löfgren's syndrome [2]. However, in Japanese patients, this syndrome is less common. In contrast, lupus pernio is very infrequent in Scandinavia, but more common among African Americans in the USA [5, 6]. On an average, ~25% of sarcoidosis cases have cutaneous involvement, which may appear at any stage of the disease [5, 9, 10]. More recently, YANARDAG *et al.* [7] reported a higher percentage (almost 33%) of skin manifestations among >500 Turkish patients. Roughly, 20% of them had EN. The frequency of reported specific cutaneous involvement in sarcoidosis ranges from 10–40%.

Systemic sarcoidosis and skin lesions

When sarcoidosis presents with EN, there will be mostly concomitant chest radiographic changes showing bilateral hilar lymphoma (stage I) and, frequently, also fever and sometimes signs of ankle arthritis, or just arthralgia. The bilateral hilar syndrome has previously been described in 1952 by LÖFGREN and LUNDBÄCK [11]. Later on, it was designated Löfgren's syndrome. Furthermore, according to MAÑÁ *et al.* [12], in sarcoidosis patients with a more insidious onset, cutaneous manifestations are also rather frequently observed at an early stage of the disorder. MAÑÁ *et al.* [12] reported the presence of cutaneous lesions at the beginning of the disease in >70% of their patients. In addition, the majority of patients had other systemic manifestations at this time as well. Nonetheless, almost one-third of patients present with only skin lesions, without any other sign of sarcoidosis. However, they are prone to the development of other organ



Fig. 1. – a) Possibly the first ever case of lupus pernio to be described (Pollaiuolo, Galleria degli Uffizi, Florence, Italy). b) Lupus pernio with typical advanced changes on the cheeks and nose in a middle-aged Caucasian female with sarcoidosis, and c) a less pronounced manifestation in a somewhat younger female.



Fig. 2. – Erythema nodosum on the lower limbs of a female patient.

involvement months to years later, calling for a close follow-up by the physician in charge for signs of systemic disease. Finally, some patients with systemic sarcoidosis may develop their skin manifestations later in the disease course.

In their study population consisting of ~200 Caucasians diagnosed with cutaneous sarcoidosis, VEIEN *et al.* [13] reported that the majority had infiltrative lesions. Moreover, they found no relationship between the extent of cutaneous manifestations and the extent of systemic disease. Many of the infiltrative lesions appeared to be of a chronic nature and were commonly associated with pulmonary changes, such as mottling and fibrosis. In patients with skin lesions, other than EN, OLIVE and KATARIA [14] found splenomegaly, hepatomegaly and lymphadenopathy in approximately one-third of these. In general, skin manifestations are associated with less delay in diagnosis than other manifestations of sarcoidosis [15].

Although not primarily skin lesions, in the conventional way of thinking, the recent and very interesting findings by HOITSMA *et al.* [16] of altered thermal threshold for warm and cold sensation in the feet and hands reflect small fibre neuropathy. This may cause all kinds of symptoms, including burns of the skin and other more or less traumatic signs referred to the skin.

Diagnostic tools

The most important way to discover skin lesions in sarcoidosis is of course by a thorough clinical investigation. Mostly, when the patient presents with EN changes on the lower limbs, the skin lesions are very obvious. In contrast, there may be an insidious onset of discrete non-itching lesions on other parts of the body, which only the observant doctor will notice. The clinical appearance may differ depending on the degree of commonly existing epidermal changes. Thus, there may be ichthyosiform manifestations, verrucous plaques, psoriasiform lesions, ulcers and hypo- or hyperpigmentation [17]. In general, skin lesions are easy to get access to and the diagnosis can be confirmed by obtaining a biopsy in most cases. However, EN is an exception.

Noncaseating epithelioid cell granulomas are mostly observed in the dermis, and sometimes in the subcutaneous tissue. To exclude other causes of skin lesions, signs of bacteria, mycobacteria and fungi should be looked for. Examination with polarised light enables identification of foreign material.

When searching for other extrathoracic manifestations by scintigraphic techniques [18], skin lesions may be registered and documented as well (fig. 3). However, there is no clinical relevance in detecting cutaneous manifestations in this way.

The differential diagnoses include, depending on the character of the lesion and what part of the world the patient comes from, disorders such as cutaneous tuberculosis, syphilis, discoid lupus erythematosus and lepromatous leprosy.

Nonspecific skin manifestation: erythema nodosum

EN is the most common nonspecific skin lesion in sarcoidosis. The entity EN was introduced over two centuries ago by Robert Willan who described the initially occurring red, rounded patches, which become elevated and painful within days. After >1 week they get more bluish and this appearance subsequently becomes less pronounced and subsides within weeks or months (fig. 2). EN associated with bilateral hilar lymphoma, fever and often arthralgia is most commonly present on the lower limbs below the knees of young females [1]. It may, however, also occur in other localisations and is occasionally noticed in males. JAMES [1], in the late 1950s, studied 170 patients with EN, and ~75% of them were female. A total of 60% of them had polyarthralgia,

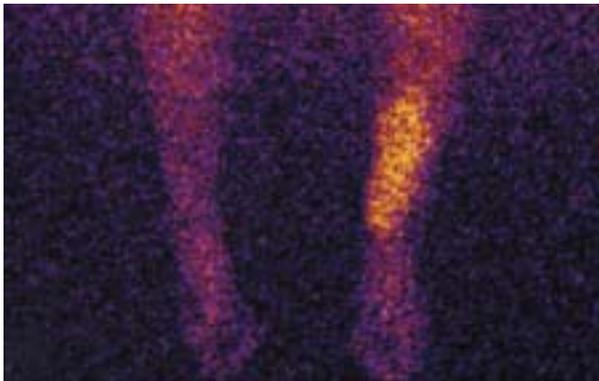


Fig. 3. – OctreoScan scintigraphy, using a long-lived radiolabelled somatostatin analogue, displaying granulomatous skin lesions on the forearms of a patient diagnosed with sarcoidosis.

predominantly in ankles and knees. The majority of this latter population consisted of patients diagnosed with sarcoidosis. Interestingly, JAMES [1] noticed that, although EN may occur at every season of the year, there is a clear predominance in Europe for late winter and early spring. The reversed phenomenon has been reported from the southern hemisphere of the globe [19].

A negative tuberculin reaction in cases with EN does not support one of the alternative diagnoses, tuberculosis. A conversion to a positive from a negative reaction strongly favours primary tuberculosis. Another fairly common cause of EN is a streptococcal infection.

The diagnosis of EN is made after physical examination, and punch biopsies should not be taken to look for noncaseating epithelioid granulomas as they are rarely present in EN. Disease onset with Löfgren's syndrome is strongly indicative of a good prognosis, but there are some cases which are not human leukocyte antigen (HLA)-DRB1*03 (DR17) positive that may have a more protracted disease course [4]. The HLA class I type may modify the class II-related disease course and the most favourable outcome seems to be in sarcoidosis patients having the deduced haplotype: A*01, B*08, DRB1*03 [20]. Once the EN changes have disappeared, they will very seldom recur after the first year has elapsed.

Specific skin manifestations

Lupus pernio

This is an indolent, red-purple or violaceous, indurated skin lesion (fig. 1a–c) that may affect cheeks, nose, lips and ears mostly in females aged >40 yrs. The lesions can range widely from small rounded manifestations to exuberant plaques covering cheeks and nose, becoming very disfiguring. Scaly desquamation may be observed, and erosions can occur. The lesions can erode into cartilage and bone and are regarded as ominous signs reflecting chronicity and poor prognosis. Lupus pernio is more often seen in Blacks than in Caucasians [5, 6, 21]. Frequently, there is concomitant involvement of the upper respiratory tract and, in aggressive cases, ulcerations in the nasal mucosa and even perforation of the septum may occur. Concomitant fibrosing changes in the lungs and bone cysts have been reported. The skin overlying bone manifestations may show similar changes, *e.g.* in the phalanxes of toes and fingers, which may be swollen. If the facial manifestations resolve there may be discrete telangiectatic scars [13].

Plaque formation

One of the most frequently encountered specific skin manifestations [12] in sarcoidosis is plaque formation (fig. 4a–c). Often the plaques are rounded or oval in shape. Their size may vary from some millimetres to several centimetres in diameter. They are usually red-brownish, indurate, and not itchy (fig. 5). They may extend in a centrifugal way leaving a centre which looks somewhat atrophic, and presents as a slightly elevated and marked margin. The process often tends to proceed over months to years and may leave disfiguring areas behind or eventually heal with remarkably little scarring. In atrophic areas, telangiectasis can be observed. Plaques have a predilection for the limbs, back, face, and scalp.

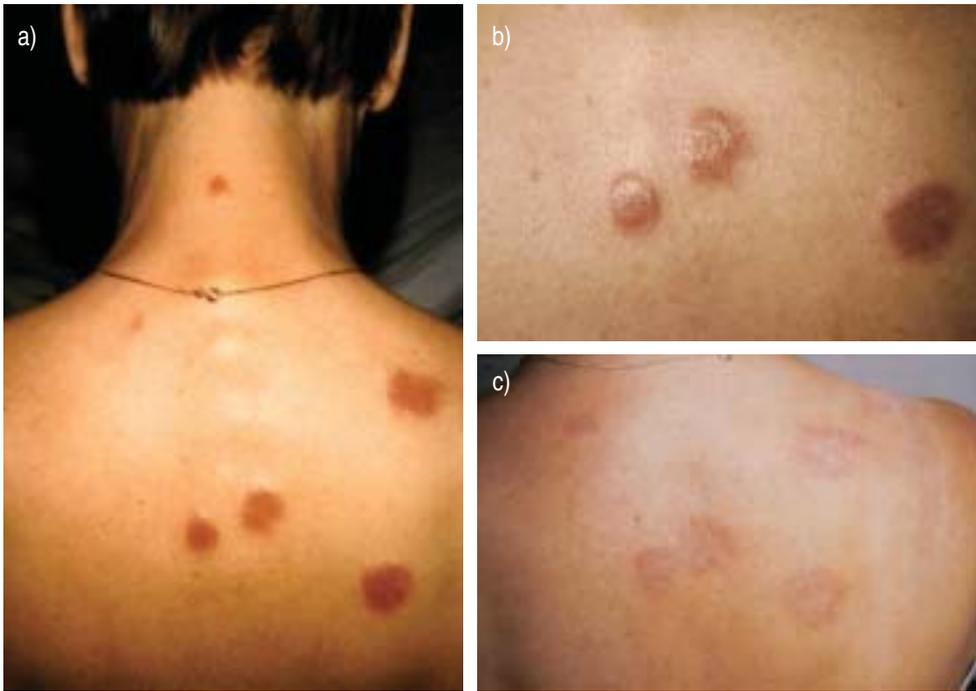


Fig. 4. – a) Brownish, rounded granulomatous plaque formations on the back of a middle-aged Caucasian female. b) The indurated, elevated character of the lesions is seen on a close up, whereas c) the depressed central part and somewhat raised rim is seen at resolution a few years later.

Maculopapular eruptions

Maculopapular lesions (fig. 6) have been reported to be the most common cutaneous manifestation of granulomatous involvement in sarcoidosis [9]. The papules are commonly red-brown to purple, slightly infiltrated and measure less than 10 mm. In contrast to lupus pernio or plaques, they are more often associated with a favourable



Fig. 5. – Plaque formation on the lower back in a male with stage I disease.



Fig. 6. – Maculopapular lesions on a knee.

outcome and can resolve in rather a short time. They may even herald the disease and can be observed almost anywhere, often in groups. In a study by MAÑÁ *et al.* [12], skin eruptions were accompanied by chest radiographic changes corresponding to stage I disease in >50% of the cases. These findings were supported by a report by YANARDAG *et al.* [7]. However, papules and nodules may also be seen in subacute and occasionally chronic phases of sarcoidosis.

Subcutaneous nodules

Similar to maculopapular lesions, subcutaneous nodules also frequently occur; according to some authors, they are most often seen in patients with stage I disease [7]. In contrast, others have found them to be less frequent and often accompanied by more systemic disease [14, 22]. The reported differences may reflect genetic heterogeneity between the investigated populations. The lesions are usually painless, firm and mobile.

Cicatricial and foreign body manifestations

Reactivation of old scar tissue has been reported in a small percentage of sarcoidosis patients [7, 23]. This may occur in scars from previous wounds (fig. 7a and b), as well as at sites of tattoos [24], sites of ritual scarification, *etc.* Skin lesions have also been reported after carbon dioxide laser resurfacing of the skin [25]. The changes may be solitary or just a manifestation of systemic disease. Reactivation of old scars, often seen as red-brownish infiltrations, seems to be a rather unique occurrence in sarcoidosis and should always call for a work-up with regard to the disease. In this context, it is important to emphasise that in a considerable part (~20–50%) of biopsies from cutaneous lesions, foreign bodies may be observed [26–28]. This is particularly common in biopsies taken from sites that are easily exposed to trauma, such as elbows and knees. Cutaneous sarcoid-like lesions without signs of systemic disease may be regarded as local-sarcoid tissue reactions. There will be cases with sarcoidal reactions in the skin despite no known trauma. In addition, lesions will be seen with signs of foreign material, but with or without demonstrable systemic disease. All patients with sarcoid-type granulomatous dermatitis should be investigated for presence of generalised granulomatous disease [29]. Diagnosis depends, on the one hand, if there are signs of granulomas at other sites, and, on the other hand, if possible causes for a local reaction can be proven [30, 31]. Cicatricial lesions may reflect the activity of the systemic disease and be used as one of several markers to monitor the disorder. Commonly scar lesions will persist more than 2 yrs after diagnosis [13].

Recently, it has been reported that highly active antiretroviral therapy in HIV patients may activate granulomatous reactions in tattoos and scar tissue as the immune system is restituted [32].

Alopecia due to sarcoidosis

There are rare reports on sarcoidosis of the scalp (fig. 8) causing local alopecia [33]. In patients with sarcoidosis getting patchy hair loss, it should be taken into consideration that there may be a relationship with the granulomatous disease.

Psoriasiform sarcoidosis

Scaly follicular skin lesions are occasionally observed in patients with histologically confirmed sarcoidosis. The skin changes can resemble those seen in psoriasis (fig. 9a and b). In addition, coexistence of sarcoidosis and psoriasis may occur [34].

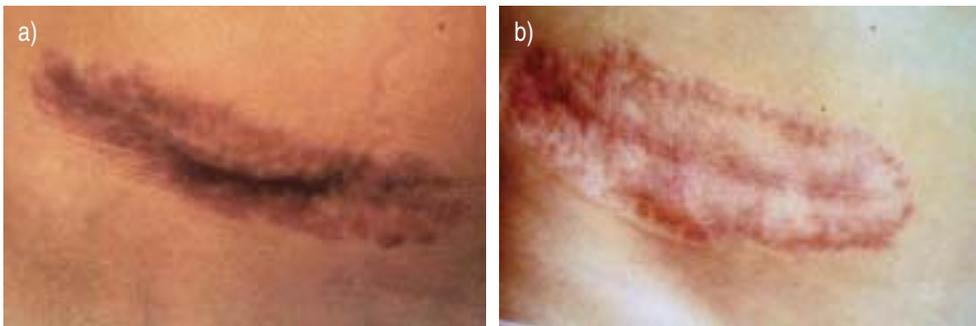


Fig. 7. – a) Granulomatous infiltration in an old scar after appendectomy in a sarcoidosis patient with multiple skin lesions. b) The scar resolved after the disease some years later. Reprinted with permission from [31].



Fig. 8. – Alopecia caused by sarcoidosis.

Granuloma annulare and sarcoidosis

Annular cutaneous lesions have been reported to occur in sarcoidosis, but granuloma annulare may also coexist with sarcoidosis, *i.e.* two granulomatous entities present in the same patient. In 1977, UMBERT and WINKELMANN [35] described five cases with coexisting disorders.

Other types of skin lesions

A number of other seldom occurring types of skin manifestations in sarcoidosis have been reported. These are partly listed in a review by ENGLISH *et al.* [9]. One of the manifestations is an ichthyosiform kind of the disease [36].

Another possible cause of cutaneous and pulmonary sarcoidosis was reported by CHANG *et al.* [37] who found granulomatous formation in papular skin lesions, superficial lymph nodes and in transbronchial biopsies in a middle-aged Chinese females who had silicone breast augmentation a few years earlier. They speculate that silicone elastomer from the implants may have leaked and caused the granulomatous reaction. Remission of sarcoidosis has been reported following removal of silicone gel breast implants [38].

There are several recent reports on cutaneous as well as systemic manifestations of

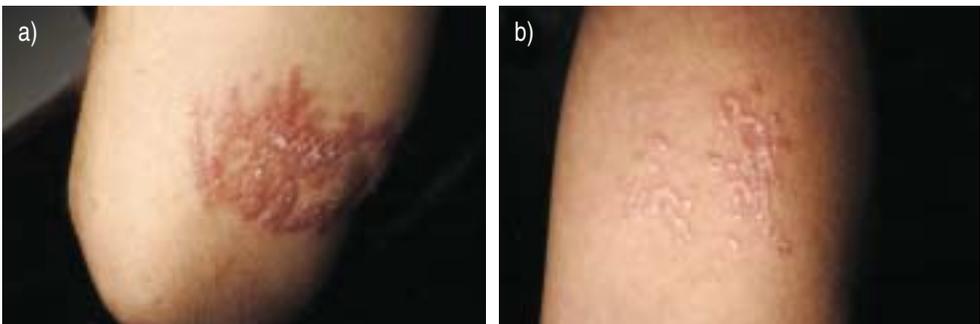


Fig. 9. – Psoriasiform skin manifestations on a) the elbow in a patient with stage I sarcoidosis, and b) scaly follicular lesions localised close to the elbow.

sarcoidosis following interferon- α (IFN) alone or in combination with ribavirin and/or amantadine, mostly in the treatment of hepatitis C [39]. IFN is regarded to increase the T-helper cell type 1 response, which is considered to be so important in granulomatous disease. It seems that patients suffering from IFN-induced skin lesions will mostly do well despite continuation of the medication that induced it.

The possibility that papular, nodular and granulomatous skin lesions in patients with suspected sarcoidosis may be manifestations of various forms of cutaneous vasculitis should also be considered [40].

Vitiligo

An association between sarcoidosis and autoimmune diseases is well-recognised. The presence of autoimmune diseases and involvement of subcutaneous fat in the sarcoid inflammation has been reported in one case but appears to represent a most unusual clinicopathological combination [41]. Vitiligo was one of the features in this reported case, and it is seen occasionally in patients with sarcoidosis (fig. 10).

Treatment

In general in systemic sarcoidosis with skin manifestations, the decision to treat will depend on associated organ involvement. Sometimes, however, especially when the cutaneous lesions are progressive and disfiguring, attempts to treat them will be made. Treatment with oral steroids given in sufficient dosage over a considerable period of time in most cases will to some extent suppress skin manifestations of a more chronic character. Such treatment will, however, also cause serious side-effects in some patients. If therapy with oral steroids is started to test the sensitivity to the drug in a specific patient, it should be kept in mind that therapy is likely to be required for a long time.

Erythema nodosum

Most patients will do well without any treatment or with just anti-inflammatory drugs given for a few weeks. In some cases, general malaise and inflammatory changes adjacent to or involving the joints in the lower limbs will call for a short course of oral steroids,



Fig. 10. – Vitiligo in a patient with sarcoidosis.

given just for a few weeks or, as an alternative, steroids could be injected in the ankles. As JAMES [1] has already pointed out, steroids may interfere with some important immune mechanisms, of which medicine was (at that time) and is presently fairly ignorant about.

Other skin lesions

No treatment. As there is no known cure as yet for sarcoidosis, treatment of harmless skin lesions or ones that are not too disfiguring, especially on limbs and the trunk, should be avoided. The manifestations seldom itch and ulcerations are fairly uncommon.

Drug treatment. Topical treatment with corticosteroids is often ineffective but some improvement may follow if complete occlusive dressings covered in clobetasol propionate lotion are used on a weekly basis to increase absorption [42]. It will take some weeks until remission occurs but the dressings seem to reduce the need for topical corticosteroids. Monthly intralesional injections of triamcinolone can be effective in treating small papules and plaques [5].

When oral steroids are prescribed, it can be in a dose which corresponds to that given for pulmonary changes (see Chapter 20 of this monograph).

As many of the facial lesions, in particular lupus pernio, are of a chronic character, the therapy, if showing a substantial beneficial effect, will have to go on for many months or even years. Hydroxychloroquine (fig. 11a and b) is an alternative to oral corticosteroids, as are methotrexate and azathioprine given in doses recommended for pulmonary changes. There are also reports on positive effects of thalidomide [43–47].

Anti-tumour necrosis factor (TNF)- α therapy is a very promising therapeutic approach of severe and therapy-resistant lesions of sarcoidosis. There is an ongoing multinational study on the efficacy of infliximab treatment in pulmonary sarcoidosis and on some extrapulmonary manifestations, such as skin lesions. The drug is a chimeric monoclonal antibody against TNF, which is thought to be a crucial player in granuloma formation. There are reports from smaller studies so far indicating that it may be an attractive treatment, acting fairly rapidly in carefully selected patients [47, 48].

The immunomodulating properties of antibiotics, beside their anti-infectious effects, have gained some interest. As no really efficient therapy of cutaneous manifestations in sarcoidosis has been reported, BACHELEZ *et al.* [49] conducted an open trial giving 12 patients minocycline (200 mg·day⁻¹) for a median duration of 12 months. Complete response was reported in eight patients, and partial in two subjects. Relapse was noticed in three patients after withdrawal. They then received doxycycline, which was followed

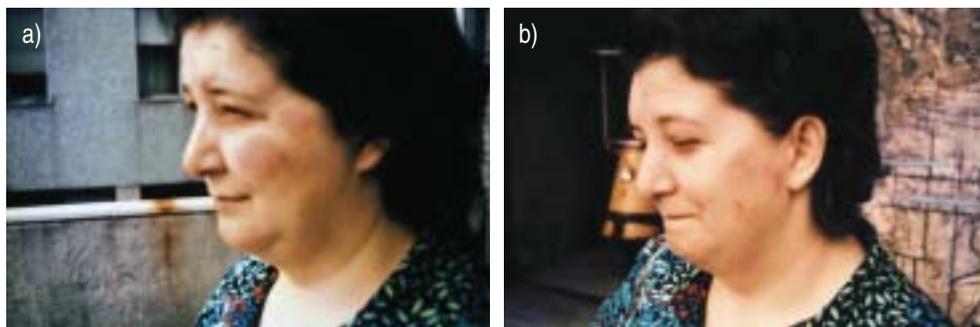


Fig. 11. – Lupus pernio a) before and b) two months after chloroquine therapy.

by remission. BACHELEZ *et al.* [49] state that randomised controlled studies to evaluate the effects are warranted.

Other therapeutic approaches. Laser. A few case reports focus on laser treatment of skin lesions in sarcoidosis. Different modalities have been used, such as the Q-switched ruby laser, pulsed dye laser and carbon dioxide (CO₂) laser [50, 51], but, at present, no definitive recommendations can be given. It should also be considered that CO₂ laser therapy has been associated with the occurrence of granulomatous reactions [24]. Therefore, this method does not seem to be clinically relevant.

Ultraviolet phototherapy. There are sporadic case reports on the effect of ultraviolet (UV) A1 phototherapy in sarcoidosis skin lesions arguing that some immunomodulating effects have been shown by UVA1 administration [52]. However, long-term risks, such as carcinogenic ones, have to be taken into account. In general, this therapy is not recommended.

Conclusion

Cutaneous lesions are present in ~25% of sarcoidosis patients. Sometimes these lesions appear to be the first manifestation and, therefore, may guide an appropriate diagnosis. The skin lesions could have specific aspects (papules, plaques, nodules, alopecia or purple scars) or can be more or less nonspecific. In general, the therapeutic approach is similar to the treatment of sarcoidosis affecting other organs, such as the lungs. It varies from none to a combination of cytotoxic agents. Therapeutic protocols are increasingly composed of multiple agents, rather than relying on a single drug.

Summary

Noncaseating epithelioid cell granulomas characterising sarcoidosis may affect most organs, including the skin. Skin lesions may be the only manifestations, or just one of several other organ involvements. Roughly 25% of all sarcoidosis patients may suffer from skin lesions during the course of their disease.

Erythema nodosum, which usually occurs at acute onset of the disease, is not characterised by granulomas and normally spontaneously resolves within weeks or months. In contrast, other skin manifestations may signal a protracted disease course. Particularly, lupus pernio may result in disfiguring lesions in the face with destruction of underlying cartilage and bone. In between these two extremes, several other types of lesions have been reported, such as red-brownish plaque formations, maculopapular eruptions, subcutaneous nodules and cicatricial manifestations. There is also a psoriasiform and an ichthyosiform of the disease.

The therapeutic approach is similar to other manifestations of sarcoidosis. The choice of drugs depends on the severity and prognosis of the lesion and whether there is any accompanying organ involvement(s).

Keywords: Cutaneous lesions, erythema nodosum, lupus pernio, sarcoidosis, skin manifestations.

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